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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/621,311	07/18/2003	Sriram Kumaraswamy	8971-032-27	3538
24510	7590	04/19/2006	EXAMINER	
DLA PIPER RUDNICK GRAY CARY US LLP ATTN: PATENT GROUP 1200 NINETEENTH STREET, NW WASHINGTON, DC 20036			KHANNA, HEMANT	
			ART UNIT	PAPER NUMBER
			1654	

DATE MAILED: 04/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b>	<b>Applicant(s)</b>	
	10/621,311	KUMARASWAMY ET AL.	
	<b>Examiner</b>	<b>Art Unit</b>	
	Hemant Khanna	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 27 February 2006.  
 2a) This action is FINAL.                    2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) Claim(s) 1-91 is/are pending in the application.  
 4a) Of the above claim(s) 17-91 is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 1-16 is/are rejected.  
 7) Claim(s) \_\_\_\_\_ is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | Paper No(s)/Mail Date. _____  |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>02/27/06</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
|   | 6) <input type="checkbox"/> Other: _____                                    |

**DETAILED ACTION**

1. Applicant's election with traverse of claims 1-16 that belong to Group I in the reply filed on February 27, 2006 is acknowledged. The traversal is on the ground(s) that inventions covered in the withdrawn claims that belong to Groups II-X are drawn to divergent subject matter which are unsupported. This is not found persuasive because the withdrawn claims are drawn to methods of either determining β-secretase activity using different assay formats or to bioconjugates and methods drawn to the determination of caspase activity. Because these inventions are distinct from the invention in Group I, searching the withdrawn inventions would be burdensome.

The requirement is still deemed proper and is therefore made FINAL.

***Specification***

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: Bioconjugates for β-secretase

***Claim Rejections - 35 USC § 103***

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

4. Claims 1-9, 11 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson et al (USPN 6627739) in view of Rosse et al (J. Comb. Chem. 2000, Vol. 2, page 461), and Jones et al (PNAS 2001, Vol. 98, page 14769).

The Anderson et al patent teaches the use of a synthetic oligopeptide with SEQ ID NO:1 containing optional detectable tags, for utility in the activity measurement of an aspartyl protease, namely,  $\beta$ -secretase (Column 51, lines 15-30). Anderson et al suggest detecting the cleavage products using fluorescent methods well known in the art. The Anderson et al patent does not explicitly teach appending a fluorescer and a quencher to the two sides of the target sequence comprising SEQ ID NO:1, nor do they show a plurality of fluorescent species capable of amplified superquenching.

Rosse et al explicitly teach the use of a cleavable peptide library on a solid support using methods known to one of ordinary skill in the art to screen for an enzyme,

Napsin A, that belongs to the same family of proteases as  $\beta$ -secretase namely, aspartyl proteases. The cleavable peptide library taught by Rosse et al comprises an enzymatic substrate located between the fluorescer and a non-fluorescent quencher (Dabsyl, Figure 2, page 462; Table 3, page 464), but which comprises a Fluorescence Resonance Energy Transfer (FRET) pair of a fluorescer (Lucifer Yellow) and a quencher (Dabsyl).

Jones et al teach a fluorescer that is a polyelectrolyte comprising a plurality of fluorescent species made up of conjugated polymers and polymers containing pendant cyanine dyes. These fluorescers are capable of amplified superquenching in presence of oppositely charged quenchers. Jones et al suggest that the use of a polymeric fluorescer in solution increases the efficiency of superquenching which is mimicked by small oligomeric fluorescers on solid supports (Abstract, Left column, page 14769). Further, Jones et al teach that the fluorescer synthesized from a series of cyanine pendant poly (L-lysine) derivatives (CDP, Left column, First paragraph, page 14769) can be adsorbed onto silica microspheres and clay nanoparticles as a means to facilitate superquenching via J-aggregation. (Right Column, Second paragraph, page 14770). Note, this aggregation of a plurality of fluorescent chromophores, onto a solid surface is also considered as a virtual polymer.

It would have been obvious to one of ordinary skill in the art to modify the oligopeptide recognized by  $\beta$ -secretase as taught by Anderson et al to form a tether

comprising the recognition sequence of SEQ ID NO:1, a plurality of fluorophores and a quencher capable of amplified superquenching as taught by Rosse et al, and Jones et al. One would have been motivated to prepare a  $\beta$ -secretase binding bioconjugate with a fluorophore and quencher because Anderson et al suggest the use of  $\beta$ -secretase screening assays based on fluorescence methods to modulate the activity of  $\beta$ -secretase for use in therapeutics in the treatment of Alzheimer's disease (Abstract, Column 51, lines 15-30). There would have been a reasonable expectation of success in view of the teachings of Anderson et al that the preparation of oligopeptides with fluorescence tags is well known in the art. Thus the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

5. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson (USPN 6627739), Rosse, and Jones et al as applied to claims 1-9, 11 and 15 above, and further in view of Stoll et al (Eur. J. Biochem. Vol. 267, page 1795).

Anderson, Rosse, and Jones et al teach as discussed above an oligopeptide recognized by  $\beta$ -secretase comprising the recognition sequence of SEQ ID NO:1, a plurality of fluorophores on solid support and a quencher capable of amplified superquenching. Anderson, Rosse, and Jones et al do not teach a fluorescer that is constructed from an oligosaccharide.

Stoll et al teach the generation of oligosaccharide probes that incorporate a fluorescent label. Although the chemical conjugation of oligosaccharides with fluorescent lipids addresses the need to detect the binding of bioactive glycans

(Abstract, Left Column, First Paragraph, page 1795), the reference shows that chemical conjugation of oligosaccharides with a fluorescer as recited in Claim 10 is a routine consideration in the art and it is obvious to choose any known fluorophore based on high extinction coefficient, ease of handling, availability and stability during derivatization procedures.

Therefore it would be obvious to one of ordinary skill in the art at the time the invention was made to have provided the teachings of Anderson, Rosse, and Jones et al with a fluorophore constructed from an oligosaccharide as taught by Stoll et al since it is a routine consideration in the art, i.e. the construction of fluorophore-linked oligosaccharide probes.

6. Claims 12-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson (USPN 6627739), Rosse, and Jones et al as applied to claims 1-9, 11 and 15 above, and further in view of Braun et al (PG PUBS 20030232420).

Anderson, Rosse, and Jones et al teach as discussed above an oligopeptide recognized by  $\beta$ -secretase comprising the recognition sequence of SEQ ID NO:1, a plurality of fluorophores on solid support and a quencher capable of amplified superquenching. Anderson, Rosse, and Jones et al do not teach the interaction of a fluorescer bound on a solid support with a protein moiety comprising neutravidin.

Braun et al teach the conjugation of peptides with detectable fluorescent labels for use in screening assays to identify compounds that modulate enzymatic activity. By providing a means to rely on screening via the preparation of bioconjugates , Braun et al

are able to select compounds for potency and selectivity towards PKA haloenzymes. Braun et al show the development of a detection system involving a biotinylated oligomeric peptide (fluorescent polymer resulting from the inclusion of a tryptophan residue in the 27-mer) immobilized on neutravidin (NA)-coated 96-well micro-titer plates (solid support) as a platform to probe for binding to PKA (Example 4, page 27).

Therefore it would be obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Anderson, Rosse, and Jones et al with a fluorophore capable of being associated with a solid support via a neutravidin tether as taught by Braun et al. One would have been motivated to prepare a fluorophore covalently linked to a protein conjugate because the teachings of Braun et al suggest the use of such conjugates as being advantageous to the development of screening assays for ultimately identifying small molecules capable of modulating enzymatic activity. There would have been a reasonable expectation of success in view of the teachings of Braun et al that those skilled in the art can make modifications to peptides for use as diagnostics of functional activity.

7. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Anderson (USPN 6627739), Rosse, and Jones et al as applied to claims 1-9, 11 and 15 above, and further in view of Ha et al (PNAS, Vol. 96, page 893)

Anderson, Rosse, and Jones et al teach as discussed above an oligopeptide recognized by  $\beta$ -secretase comprising the recognition sequence of SEQ ID NO:1, a

plurality of fluorophores on solid support and a non-fluorescent quencher, namely Dabsyl. Anderson, Rosse, and Jones et al do not teach a fluorescent quencher.

Ha et al teach the conjugation of Staphylococcal nuclease (Snase) with a quencher made up of a fluorescent cyanine dye, Cy5 (Right Column, Second Paragraph, page 893) to observe the catalytic reactions of enzymes. Further, Ha et al teach that FRET techniques are useful for studying aspects of enzyme catalysis that rely on being able to provide information on substrates for enzymes.

Therefore it would be obvious to one of ordinary skill in the art at the time the invention was made to have modified the teachings of Anderson, Rosse, and Jones et al with a fluorescent quencher as taught by Ha et al. One would have been motivated to prepare a protein-fluorescent quencher conjugate because Ha et al suggest the conjugation of quenchers with proteins for studying complex aspects of enzymatic events comprising protein-inhibitor binding (Left Column, Third Paragraph, page 893).

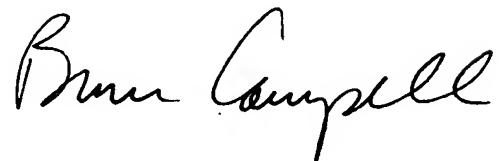
### ***Conclusion***

7. No claim is allowed.
8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hemant Khanna whose telephone number is (571) 272-9045. The examiner can normally be reached on Monday through Friday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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